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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,822	BAKER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-35 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-35 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07 August 2006 has been entered.

Status of Application, Amendments and/or Claims

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 28-35 and 38-40 are under consideration in the instant application.

Information Disclosure Statement

The information disclosure statement submitted on 07 August 2006 has been fully considered. It is noted that citations crossed off by the Examiner have been cited in duplicate.

Claim Rejections - 35 USC § 101 and 35 USC § 112

1. Claims 28-35 and 38-40 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation. The basis for this rejection is set forth for claims 28-35 and 38-40 at pg 2-19 of the Office Action of 30 November 2005, at pg 3-12 of the Office Action of 25 April 2005, and at pg 3-8 of the Office Action of 04 November 2004.

Specifically, claims 28-35 and 38-40 are directed to an isolated polypeptide having at least 80%, 85%, 90%, 95%, and 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide shown of SEQ ID NO: 374, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 374, lacking its associated signal peptide, or (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203465; wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors. The claims also recite a chimeric polypeptide comprising a polypeptide fused to a heterologous polypeptide.

Applicant's arguments (07 August 2006), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At pg 6-7 of the 07 August Response, Applicant asserts that it was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Applicant states that Example 143 of the specification discloses that the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8. Applicant explains that a ΔCt value of at least 1.0 was observed for PRO1759 in at least three of the tumors listed in Table 8. Applicant argues that PRO1759 showed approximately 1.11-1.51 ΔCt units which corresponds to $2^{1.11}$-$2^{1.51}$ fold amplification or 2.16 fold or 2.85 fold amplification in lung tumors HF000842 and HF001296 and in colon tumor center HF000795. Applicant submits that the specification has not only disclosed that the DNA copy number for the gene encoding PRO1759 is increased in *three different lung tumors*, but has also quantified the degree of gene amplification observed in each of these lung tumors.

Applicant's arguments have been fully considered but are not found to be persuasive. In the instant case, the specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue (lung and colon). However, there is no evidence regarding whether or not PRO1759 mRNA or polypeptide levels are also increased in these cancers. Further research needs to be done to determine whether the small increase in PRO1759 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. It is not known whether PRO1759 is expressed in corresponding normal tissues, and what the relative levels of expression are. For example, the gene amplification data presented in the specification were problematic. The control DNA appeared to be from blood rather than from a matched tissue sample (i.e., healthy lung and colon), while the literature shows that matched tissue samples are the standard (Pennica et al.; cited in the Office Action of 04 November 2004). Also, the data were not corrected for aneuploidy, a phenomenon that occurs in cancerous and non-cancerous lung (Sen; cited in the Office Action of 04 November 2004). Therefore, it is not clear that the reported amplification is significant. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1759 is amplified in a variety of samples and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment. This further experimentation is part of the act of

invention and until it has been undertaken, Applicant's claimed invention is incomplete (see *Brenner v. Manson*, (1966, 383 U.S. 519, 148 USPQ 689)).

(ii) At pages 7-8, 15-16 of the 07 August 2006 Response, Applicant asserts that the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Applicant argues that the references cited by the Examiner (Pennica et al, Chen et al., Haynes et al., Hu et al., Madoz-Gurpide et al., Celis et al., Steiner et al., and Feroze-Merzoug et al.) do not suffice to make a *prima facie* case that more likely than not generalized correlation does not exist between increased mRNA expression and increased polypeptide levels. Applicant states that the burden to rebut the rejection based on alleged lack of patentable utility has not properly shifted to Applicant. Applicant contends that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited references and application of an improper, heightened legal standard. Applicant states that the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

Applicant's argument has been fully considered but is not found to be persuasive. The truth, or credibility, of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not substantial. In the previous Office Actions of 06 October 2005, 25 April 2005, and 04 November 2004, the Examiner made a *prima facie* showing that the claimed invention lacks utility and provided sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing (Pennica et al., Sen et al., Chen et al., Haynes et al., Hu et al., Madoz-Gurpide et al., Celis et al., and Feroze-Merzoug et al.). These references,

taken into consideration with the disclosure, indicate to the skilled artisan that it is more likely than not that PRO1759 polypeptide is not useful as a cancer diagnostic agent. Essentially, Applicant has not provided evidence to demonstrate that the PRO1759 polypeptide of the instant application is supported by a specific and asserted utility or a well established utility. The Examiner has fully considered all evidence of record and has responded to each substantive element of Applicant's response (see points (i) and (iii)-(xvi)). It is noted to Applicant that MPEP § 2107.02 (part VI) also states that "only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained".

(iii) At pg 8 of the Response, Applicant indicates that the teachings of Pennica et al. are specific to *WISP* genes and say nothing about the correlation of gene amplification and protein expression in general.

Applicant's argument has been fully considered but is not found to be persuasive. As discussed in the previous Office Action of 25 April 2005, the instant specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue (lung and colon) (pg 517-519). However, there is no evidence regarding whether or not PRO1759 mRNA or polypeptide levels are also increased in these cancers. Furthermore, what is often seen is a *lack* of correlation between DNA amplification and increased peptide levels (Pennica et al.). Pennica et al. and Sen et al. establish that gene amplification is a general feature of cancer, and that it is not predictable that the amount of amplification seen for PRO1759 is predictive of protein levels, and hence the protein lacks a readily available utility. While Pennica et al. is

directed to small numbers of genes, the instant application only concerns one gene and the protein it encodes. Applicant has not provided any testing of the role, activity, or expression of the PRO1759 polypeptide in cancer. The art as a whole teaches toward a *lack of expectation* of a correlation for a gene that is amplified consistent with the data proffered for PRO1759.

Furthermore, as discussed by Haynes et al., polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. As discussed above, Hu et al. analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (pg 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Similarly, Chen et al. disclose that twenty-eight of the 165 protein blots (17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression (see Abstract and Table I). In addition, their results showed that no significant correlation between mRNA and protein expression was found ($r = -0.025$), if the average levels of mRNA or protein among all samples were applied across the 165 protein blots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In this

study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is showed that only a minority subset of the proteins exhibited a significant positive correlation with mRNA abundance.

As supported by the studies cited above, the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels. Madoz-Gurpide et al. (Adv Exp Med Biol 532: 51-58, 2003) even indicate that "[f]or most of the published studies it is unclear how well RNA levels reported correlate with protein levels. A lack of correlation may imply that the predictive property of the gene(s) is independent of gene function" (pg 53, 1st full paragraph). However, the specification of the instant application has only disclosed that the PRO1759 polynucleotide is slightly overexpressed (about 2-fold) in 3 lung and colon tumor samples. The specification does not indicate that the PRO1759 polypeptide has been overexpressed in the lung and colon tumor samples tested. Celis et al. emphasize that proteins are frequently the functional molecules and, therefore, the most likely to reflect differences in gene expression (pg 6, bottom of col 1). Celis et al. continue to explain that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (pg 6, col 2). Madoz-Gurpide et al. indicate that there is a need to utilize protein microarray strategies to address the many different features of proteins, including the determination of protein levels in biological samples (pg 53, 2nd full paragraph). There is also intense interest in the scientific field in applying proteomics to disease marker identification and such approaches include comparative analysis of protein expression in normal and cancer tissues

to identify aberrantly expressed proteins that may represent novel markers (Madoz-Gurpide et al., pg 54, 2nd full paragraph).

Therefore, given the small increase in DNA copy number of PRO1759 in only three tumor samples, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels. Further research needs to be done to determine whether the small increase in PRO1759 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete (*Brenner v. Manson* 1966, 383 U.S. 519, 148 USPQ 689).

The Examiner maintains that, for reasons cited above, it is more likely than not that the claimed PRO1759 protein does *not* possess the urged diagnostic utility. The art clearly shows that such a correlation occurs for only a small minority of genes that are amplified at levels consistent with those shown for PRO1759.

(iv) At page 8-9 of the Response, Applicant contends that the data in Haynes et al. confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Applicant adds that Haynes did not say that for a single gene, a change in the level of mRNA transcript is not positively correlated with a change in the level of protein expression.

Applicant argues that one cannot look at the level of mRNA across several different genes to investigate whether a change in the level of mRNA for a particular gene leads to a change in the level of protein for that gene.

Applicant's arguments have been fully considered but are not found to be persuasive. This has been fully considered but is not found to be persuasive because Haynes et al. clearly state "[p]rotein expression levels are not predictable from the mRNA expression levels" (pg 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (pg 1870, under concluding remarks). Feroze-Merzoug et al. (Cancer and Metastasis Rev 20: 165-171, 2001) disclose that "[t]he lack of correlation between mRNA and corresponding protein is evident even in low eukaryotic cells such as yeast. Therefore, it will be necessary to profile both mRNA and protein for a complete picture of how cells are altered during malignant transformation" (pg 168, col 1). Madoz-Gurpide et al. also disclose that "[f]or most of the published studies it is unclear how well RNA levels reported correlate with protein levels" (pg 53, 1st full paragraph). Clearly, Haynes et al., Feroze-Merzoug, and Madoz-Gurpide et al. indicate that mRNA levels do not predict protein levels.

It is also noted that the specification of the instant application does not teach a change in DNA, mRNA, or protein level of PRO1759. The specification simply discloses a static measurement of PRO1759 DNA in three colon and lung tumor samples as compared to a blood control. There are no teachings in the specification as to the differential expression of PRO1759 DNA, mRNA, or protein in the progression of colon or lung cancers or in response to different treatments of hormones (for example). Therefore, the Examiner maintains that Applicant's

measurement of a slight increase of PRO1759 DNA does not provide a specific and substantial utility for the encoded protein.

(v) Applicant argues at pg 9-11 of the Response that Gygi et al. (submitted as Exhibit 1 in the response of 30 November 2005) indicate a general trend of correlation between protein [expression] and transcript levels. Applicant concludes that the Gygi data meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein.

Applicant's arguments have been fully considered but are not found to be persuasive. While Gygi et al. does not address whether changes in mRNA levels will be reflected as observable changes in protein levels, the reference nonetheless demonstrates that observed mRNA levels do not necessarily correspond to observed protein levels. Gygi et al. state "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient" (abstract; pg 1727, top of col 2; pg 1730, concluding sentence).

(vi) At pg 10-11 of the Response, Applicant also asserts that Futcher et al. (1999) conducted a study of mRNA and protein expression in yeast and report a good correlation between protein abundance, mRNA abundance, and codon bias. Applicant's arguments have been fully

considered but are not found to be persuasive. Futcher et al concludes that "[t]his validates the use of mRNA abundance as a rough predictor of protein abundance, at least for relatively abundant proteins [emphasis added]" (pg 7368, col 1). Futcher et al. also admits that Gygi et al. performed a similar study and generated similar data, but reached a different conclusion. Futcher et al. indicates that "Gygi et al. feel that mRNA abundance is a poor predictor of protein abundance" (pg 7367, col 1, 1st full paragraph).

(vii) Applicant argues at pg 11 of the Response of 07 August 2006, Applicant states that Feroze-Merzoug et al. looked at androgen regulated genes, which were not necessarily associated with cancer. Applicant indicates that even if the teaching of Feroze-Merzoug et al. accurately reflects the correlation between mRNA and protein, it does not apply to the cancer diagnostic assays of the present application. At pg 10, Applicant asserts that Feroze-Merzoug et al. (cited by Examiner in previous Office Action) are focusing on "accurately predicting" the precise levels of protein expression, which is not required for utility as a cancer diagnostic.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner is unable to locate where the Feroze-Merzoug et al. reference discusses "accurately predicting" the precise levels of protein expression. Applicant has not specifically pointed out this teaching in the reference. Feroze-Merzoug et al. review recent mRNA and protein expression profiling studies performed in prostate cancer. The reference discloses that "downstream genes in the androgen pathway play a critical role in the development of hormone-refractory prostate cancer" (pg 166, col 1, 1st paragraph). Thus, even though Feroze-Merzoug et al. do not examine the expression of PRO1759 of the instant application, the teachings of Feroze-

Merzoug et al. clearly indicate that mRNA levels do not predict protein levels. For example, Feroze-Merzoug et al. disclose that "there is evidence highlighting the disparity between mRNA transcript and protein expression levels" and that "it will be necessary to profile both mRNA and protein for a complete picture of how cells are altered during malignant transformation" (pg 168, col 1, 1st full paragraph).

(viii) At page 11-12 of the 07 August 2006 Response, Applicant further asserts that the analysis of Chen et al. is not applicable to the instant application. Applicant indicates that the Chen paper does not account for different expression in different tissues or different stages of cancer. Applicant argues that a review of the actual data presented in Tables I and II of the Chen paper demonstrates that it is more likely than not that protein levels will correlate with mRNA expression levels.

Applicant's arguments have been fully considered but are not found to be persuasive. Chen et al. compared mRNA and polypeptide expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). The instant specification does not provide additional information regarding whether or not PRO1759 mRNA or polypeptide is overexpressed in lung or colon tumors, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. The

specification of the instant application also does not provide any information on the difference of PRO1759 expression in different tissues or different stages of cancer. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

(ix) At page 12 of the 07 August 2006 Response, Applicant argues that the same authors as Chen et al. published a later paper (Beer et al., Nat Med 8(8): 816-824, 2002) which described gene expression of genes and adenocarcinomas and compared that to protein expression. Applicant concludes that the authors of the Chen et al. paper agree that microarrays provide a reliable measure of the expression levels of the gene and can be used to identify genes whose overexpression is associated with tumors.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Beer et al. generated gene-expression profiles for 86 primary lung adenocarcinomas, including 67 stage I and 19 stage III tumors, as well as 10 non-neoplastic lung samples (pg 816, col 1). Beer et al. determined transcript abundance using custom algorithms and the data set was trimmed of genes expressed at very low levels. Beer et al. used hierarchical clustering to examine similarities among lung adenocarcinomas in their patterns of gene expression and even identify "three clusters that showed significant differences with respect to tumor stage and tumor differentiation" (pg 822, 1st full paragraph). However, the specification of the instant application does not disclose any special feature, stage, or prognosis, of lung tumors or colon tumors that amplify the PRO1759 gene compared to lung and colon tumors that do not amplify the PRO1759 gene. It is left to the skilled artisan to determine the significance (if

any) of such a difference. Such constitutes the type of further research required to bestow a substantial utility on the claimed invention. Furthermore, as emphasized by the state of the art (see for example, Madoz-Gurpide et al., Steiner et al., Celis et al., and Feroze-Merzoug et al.), Beer et al. complemented their DNA microarray expression studies with northern blot hybridization and immunohistochemistry experiments for three arbitrarily selected genes with high expression. However, the specification of the instant application does not complement the low (2-fold) PRO1759 gene expression data with any mRNA or protein studies. The skilled artisan would not reasonably assume that PRO1759 polypeptide is overexpressed in certain lung or colon tumors based on the disclosure regarding gene amplification without actually testing for PRO1759 polypeptide overexpression. It is also noted that Beer et al. did not examine any expression profiles of the claimed PRO1759 polypeptide or the polynucleotide encoding the polypeptide.

(x) At pg 12-13 of the Response of 07 August 2006, Applicant argues that while proteomics is a complementary technology to DNA microarrays, this does not mean that proteomic experiments are required in addition to measurements of mRNA levels to determine protein expression. Applicant states that while additional information may be useful in elucidating the detailed biological function of a protein, it is not required to establish utility of a protein as a marker for cancer. Applicant submits that Madoz-Gurpide et al. only state that it is unclear how well RNA levels reported correlate with protein levels. Applicant states that understanding the disease at the mechanistic level is not relevant to Applicant's assertions of utility. At pg 13-14 of the Response, Applicant cites Celis et al. (cited previously by Examiner) and indicates that

significant correlations between gene and protein expression are most likely to be observed for genes associated with cancer.

Applicant's arguments have been fully considered but are not found to be persuasive. Madoz-Gurpide state that "numerous alterations may occur in proteins that are not reflected in changes at the RNA level" (pg 53, 2nd full paragraph). Madoz-Gurpide et al. continue to disclose that "[u]nlike DNA microarrays that provide one measure of gene expression, namely RNA levels, there is a need to implement protein microarray strategies that address the many different features of proteins including determination of their levels in biological sample..." (pg 53, 3rd full paragraph). Madoz-Gurpide et al. do state that numerous published studies using DNA microarrays justify the use of this technology for uncovering patterns of *gene expression*. The reference does not state that the published studies using DNA microarrays uncover patterns of *protein expression*. Furthermore, Madoz-Gurpide et al. disclose that most published tumor studies using DNA microarrays have either examined a pathologically homogeneous set of tumors to identify clinically relevant subtypes, for example survivors vs non-survivors, or pathologically distinct subtypes belonging to the same lineage, for example limited stage vs advanced stage tumors to identify molecular correlates, or tumors of different lineages to identify molecular signatures for each lineage (pg 52, 1st paragraph).

Additionally, although proteomics is a complementary technology to DNA microarrays, it is quite clear that the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels. Celis et al. emphasize that proteins are frequently the functional molecules and, therefore, the most likely to reflect differences in gene expression (pg 6, bottom of col 1). Celis et al. continue to explain that "[g]enes may be present, they may be mutated, but

they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (pg 6, col 2). As mentioned at pg 6 of the Office Action 06 October 2005, Madoz-Gurpide et al. teach that there is also intense interest in the scientific field in applying proteomics to disease marker identification and such approaches include comparative analysis of protein expression in normal and cancer tissues to identify aberrantly expressed proteins that may represent novel markers (pg 54, 2nd full paragraph).

(xi) At pg 13 of the Response of 07 August 2006, Applicant argues that the study by Steiner et al. (cited previously by Examiner) is limited to the role of proteomics in drug development and toxicology testing and does not even discuss cancer or diagnostics.

Applicant's arguments have been fully considered but are not found to be persuasive. Steiner et al. was cited by the Examiner previously to indicate that the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels. Although Steiner et al. review proteomic applications in general pharmaceutical development, Steiner et al. state that "[i]nformation about (i) post-translational modifications critical to our understanding of proper physiological protein function, (ii) subcellular localization, and (iii) protein translocation can be obtained only by profiling proteins, not by profiling mRNA. Most important is the growing evidence of the poor correlation between mRNA and protein abundance" (pg 2100, col 1, first full paragraph). Steiner et al. disclose that protein profiling of expressed genes in tissues and cells is more likely to lead to a better understanding of cellular regulation, give better insight into

disease, and that mRNA profiling should be combined with appropriate protein measurements (pg 2100, col 1, first full paragraph).

(xii) Regarding Hu et al., Applicant indicates that among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. At pg 14-15 of the 07 August 2006 Response, Applicant argues that Hu et al. does not conclusively show that it is more likely than not that the gene amplification does not result in increased expression at the mRNA and polypeptide levels. Applicant contends that since Hu et al. only studies the statistical analysis of microarray data and not the gene amplification data, their findings would not be directly applicable to the gene amplification data. Applicant also states that Hu et al. manipulated various aspects of the input data. Applicant urges that a paper to a particular type of breast tumor cannot be generalized as a principle governing microarray study of breast or other cancers in general. Applicant is urging an improper standard.

Applicant's arguments have been fully considered but are not found to be persuasive. The asserted utility for the claimed polypeptides is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold

change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. The instant specification does not disclose that PRO1759 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO1759 protein can be used as a cancer diagnostic. Regarding Applicant's criticism of Hu et al.'s statistical analysis, Applicant is holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc. Regarding Applicant's criticism of Hu et al. as being limited to a specific type of breast tumor, Hu et al. is cited as one of several pieces of evidence that gene amplification in a tumor does not correlate with mRNA overproduction or protein overproduction. Applicant repeatedly tries to impugn references for being drawn to different genes than PRO1759, or different types of cancers, but have provided no more "relevant", e.g. closer to the instant fact situation, data or references. Accordingly, the record must be judged for what the cited references teach. When viewed with the evidence of record as a whole, there is no correlation between gene amplification, mRNA levels and protein levels. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

(xiii) At pg 15-16 of the 07 August 2006 Response, Applicant asserts that the Patent Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or

credible. Applicant contends that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited references and application of an improper, heightened legal standard. Applicant states that the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

Applicant's arguments have been fully considered but are not found to be persuasive. The truth, or credibility, of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not substantial. The preponderance of evidence supports this position. See Pennica et al., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associated with breast cancer), Haynes et al., Feroze-Merzoug et al., Madoz-Gurpide et al., Steiner et al., and Celis et al. These references, taken into consideration with the disclosure, indicate to the skilled artisan that it is more likely than not that PRO1759 polypeptide is not useful as a cancer diagnostic agent.

(xiv) At pages 16 of the 07 August 2006 Response, Applicant argues that Orntoft et al., Hyman et al. and Pollack et al. teach that, in general, gene amplification correlates with increased mRNA expression. Applicant points to the Polakis declaration (submitted under 37 C.F.R. § 1.132 on 02 February 2005) as establishing that there is a general correlation between mRNA levels and polypeptide levels. Finally, Applicant concludes that, while there may be exceptions, there is generally a good correlation between gene amplification, mRNA levels and polypeptide levels,

and thus the gene amplification data for PRO1759 conveys utility to the claimed anti-PRO1759 antibodies.

Applicant's arguments have been fully considered but are not found to be persuasive. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). Orntoft et al.'s findings could only be extended to other genes in such clusters. This analysis was not done for PRO1759 in the instant specification, and so it is not clear whether or not PRO1759 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the findings of Orntoft et al. cannot be extended to PRO1759. Also, Orntoft et al. compared genes from non-invasive transitional cell carcinomas to genes from invasive transitional cell carcinomas. There was no comparison between genes in cancerous versus non-cancerous tissue. Thus, Orntoft et al. did not find any cancer markers. Furthermore, Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins. (See abstract). Applicant has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Finally, Orntoft et al. did not study lung or colon cancer.

Hyman et al. found 44% (less than half) of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. It is noted that Hyman defines (Fig. 1A) highly amplified genes as greater than 2.5 CGH (normalized to housekeeping genes). This is direct evidence that it is "more likely than not" that

gene amplification does *not* correlate with increased mRNA expression. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1759 would be correlated with elevated levels of mRNA, much less protein. Also, Hyman et al. did not evaluate lung or colon cancer. It is further noted that Hyman standardized to 88 housekeeping genes (p. 6241, left column); the instant specification includes no such standardization. Thus, comparing Hyman's data to Applicant, it can be concluded that PRO1759 was not assayed in a fashion that one could conclude it to be "highly amplified" as the term is used by Hyman.

Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. Also, Pollack et al. did not study lung or colon cancer. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung or colon cancer.

Regarding the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 with the response filed 02 February 2005, Applicant characterizes the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Applicant concludes that all of the submitted

evidence supports Applicant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. The declaration of Dr. Polakis was previously considered by the Examiner in the Office Action of 25 April 2005. Applicant's arguments and the Polakis declaration have been fully considered but are not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949). (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. There is no specific indication in the Polakis declaration that PRO1759 mRNA was elevated and correlated with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO1759 (i.e., data regarding amplification of PRO1759 genomic DNA), and does not disclose any information regarding PRO1759 mRNA or protein levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased

mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Hu et al., Haynes et al., Chen et al., Feroze-Merzoug et al., Madoz-Gurpide et al., Steiner et al, Celis et al., discussed *supra*. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

It remains that for the PRO1759 gene, a 2.16 to 2.85 fold amplification of the genomic DNA has been shown for three tumors/tumor cell lines. There has been *no* demonstration of the existence of any mRNA nor the level thereof, nor any demonstration of any protein expression, in any cell or tissue, under any conditions. In view of the cited art, the Examiner maintains that the data in the specification would not be considered by one skilled in the art to be reasonably predictive that the claimed proteins have diagnostic or prognostic utility.

(xv) At pg 16-17 of the 07 August 2006 Response, Applicant refers to the second declaration of Dr. Polakis (Polakis II), submitted with the response. Dr. Polakis declares that 28 of 31 genes identified as being detectably over expressed at the mRNA level were found also to have increased protein levels.

The second Polakis declaration under 37 CFR § 1.132 filed 07 August 2006 is insufficient to overcome the rejection of claims 28-35 and 38-40 based upon 25 U.S.C. §§ 101 and 112, first paragraph, for the following reasons. Specifically, there is no demonstration of *any* mRNA level for PRO1759, hence the theoretical correlation of mRNA with protein is not

probative. For example, the data for PRO1759 does not seem appear in the table (Exhibit B). It is not clear which "UNQ" number refers specifically to PRO1759, if any at all. Furthermore, it is not clear if the results presented in the table were determined by the same methodology as presented in Example 143 of the instant specification. For example, how highly expressed were the genes in Exhibit B that purportedly correlate with increased protein levels, 2-fold, 5-fold, 10-fold? How many samples were used? By what means was the level of mRNA expression determined, e.g., microarray, Northern blot, quantitative PCR? Were *matched* tissue controls used? The declaration only states that levels of mRNA and protein in tumor tissue were compared to normal tissue.

Additionally, the Examiner notes that the two Polakis declarations are not consistent. In the first declaration, Dr. Polakis declares that "we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells". In the second, he states that "we have identified approximately 200 gene transcripts that are present in human tumor *tissue* at significantly higher levels than in corresponding normal human *tissue*."

In the first declaration, Dr. Polakis declares that "In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells." In the second, he states that "of the 31 genes identified as being detectably overexpressed in human tumor tissue as compared to normal human tissue at the mRNA level, 28 of them (i.e. greater than 90%) are also detectably overexpressed in human tumor tissue as compared to normal human tissue at the protein level."

It cannot be determined whether the two declarations are referring to the same data set, or different data sets. Further, there has been no explanation of why the Declarant now refers to tumor *tissue* rather than tumor *cells,* nor what the perceived significance of this change is.

(xvi) At pg 18 of the Response of 07 August 2006, Applicant has submitted teachings from Alberts, B. (Molecular Biology of the Cell (3rd ed 1994 and 4th ed 2002)) and Lewin, B. (Genes VI 1997) to support the statements of Dr. Polakis (Polakis II declaration; (point (xii) above). At pg 18-25, Applicant also cites numerous references to emphasize that those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression (such as Zhigang et al., Meric et al. Wang et al., Munaut et al., Hui et al., Khal et al., etc.). Applicant asserts that changes in mRNA level for a particular gene generally lead to corresponding changes in the level of expressed protein. Applicant also contends that the references and the Polakis declaration establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Applicant's arguments have been fully considered but are not found to be persuasive. While the Examiner acknowledges the teachings of Alberts and Lewin, which disclose that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA

degradation control mechanisms (see Alberts 3rd ed., bottom of pg 453). Meric et al. states the following:

> "The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription."

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974). Celis et al. also teach that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (pg 6, col 2).

Applicants have submitted a voluminous new information disclosure statement, with 149 references, purportedly to show that genomic DNA, as measured for PRO1759, is predictive of protein levels. A number of Applicant's arguments continue to be, and the vast majority of newly cited references are, directed at the predictability of protein levels when *mRNA* levels are amplified. The Examiner maintains that the most significant issue in this case is that the data are drawn to *genomic* data, and *not* mRNA data.

Furthermore, all of Applicant's newly cited references (with the exception of Bea et al. and Godbout et al.) do not measure gene amplification, which is the assay utilized in Example 143 of the instant specification. Also, with the exception of Futcher et al., all of Applicant's

newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. The studies cited by Applicant that examine the expression of specific genes or small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined and more accurately describe general trends, specifically, Haynes (80 proteins examined) and Chen (165 proteins examined) (cited previously by Examiner).

At the bottom of pg 24 through pg 25, Applicant indicates that Bea et al. investigated gene amplification, mRNA expression, and protein expression of the putative oncogene BMI-1 in human lymphoma samples. Applicant argues that four tumors with gene amplification of BMI-1 showed significantly higher levels of mRNA and protein expression. Applicant argues that the issue is not whether mRNA overexpression is always, or even typically caused by gene amplification, but rather, whether gene amplification typically leads to overexpression. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, out of 262 human tumors, Bea et al. identified *BMI-1* gene amplification, increased mRNA, and increased protein levels in only four mantle cell lymphoma tumors (MCL) (pg 2411, col 1). Table 1 at pg 2410 even teaches that out of 36 MCL tumor samples, only four samples with gene amplification of BMI-1 showed significantly higher levels of mRNA and protein expression. Bea et al. teaches that no alterations were detected in any of the different types of carcinoma studies and that the findings indicate that *BMI-1* gene alterations in human neoplasms are an uncommon phenomenon, but seem to occur in a subset of non-Hodgkin's lymphoma, particularly mantle cell type (pg 2411, bottom of col 1 through the top of col 2). It is noted that the study of Bea et al. is directed to one particular gene (BMI-I) and specific cancer types and

does not accurately describe general trends. Bea et al. also performed Southern blots, RT-PCR, and Western blots to determine the relationship between gene amplification, mRNA expression, and protein expression, which is unlike Example 143 of the instant specification. Thus, based on the teachings of Bea et al., indicate to the skilled artisan that it is more likely than not that PRO1759 polypeptide is not useful as a cancer diagnostic agent.

Applicant indicates that Godbout et al. is a study which is more closely related to Applicant's asserted utility. At pg 25 of the Response, Applicant argues that according to Godbout et al., DDX1 gene copy number, mRNA and protein levels are correlated in cancer cell lines. However, the Examiner finds Applicant's interpretation of the reference to be erroneous. Far from teaching predictability for expression of PRO1759 on the basis of a minor genomic amplification, the abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell* (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4,

SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." Thus, Godbout et al. supports the Examiner's assertion that it is more likely than not that the PRO1759 protein would *not* be expected to be found in increased amounts in the cells tested by Applicant, and thus has no utility as a cancer diagnostic. It is also noted that regarding the instant application, there is no structure/function analysis in the specification regarding the putative protein encoded by the PRO1759 gene. It is not disclosed, and based upon the sequence searches in this case, the Examiner can not find any reason to suspect, that the protein encoded by the PRO1759 gene would confer any selective advantage on a cell expressing it. It has no known homology to any other protein that would be expected to confer a selective advantage to a tumor cell. Further, it cannot be determined from the Godbout abstract whether the level of genomic amplification of the DDX1 gene was comparable to that disclosed for PRO1759.

An additional reference that provides evidence that gene amplification does not predictably or even predominantly lead to increased transcript is Li et al., Oncogene, Vol. 25, pages 2628-2635, 2006. Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "*In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels*, implying that at least some of these genes are 'passenger' genes that

are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma.*"

Furthermore, the Examiner maintains the previous argument of record, namely that mRNA levels are not necessarily predictive of protein levels. Regarding Applicants' arguments at pg 8, 14-15, and 26 of the 07 August 2006 Response (that a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein), the specification of the instant application does not teach a change in DNA, mRNA, or protein level of PRO1759. The specification simply discloses a static measurement of PRO1759 DNA in three colon and lung tumor samples as compared to a blood control. There are no teachings in the specification as to the differential expression of PRO1759 DNA, mRNA, or protein in the progression of colon or lung cancers or in response to different treatments of hormones (for example). Therefore, the Examiner maintains that Applicant's measurement of a slight increase of PRO1759 DNA does not provide a specific and substantial utility for the encoded protein, or an antibody to the protein.

In conclusion, in the instant case, the asserted utility that PRO1759 polypeptides are useful as diagnostic markers for cancer is not substantial in that further research is required to reasonably confirm a real world context of use. In order for PRO1759 polypeptide to be useful as a cancer diagnostic, there must be a detectable change in the amount or form of PRO1759 polypeptide between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al.), and (2) increased mRNA levels do not reliably correlate with increased polypeptide levels in healthy tissue or cancerous tissue (see Haynes et al., Hu et al., Hanna et al.,

Chen et al., Feroze-Merzoug et al., Madoz-Gurpide et al., Steiner et al, Celis et al.). In view of this, the skilled artisan would have viewed the gene amplification results as preliminary with respect to the utility of the encoded polypeptides, and would have had to experiment further to reasonably confirm whether or not the claimed PRO1759 polypeptides can be used as a cancer diagnostic agent.

35 U.S.C. § 112, first paragraph (Enablement)

2. Claims 28-35 and 38-40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth at pg 19-20 of the previous Office Action (06 October 2005), pg 12-15 of the Office Action of 25 April 2005 and at pg 8-11 of the Office Action of 04 November 2004.

Applicant's arguments (07 August 2006), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant states that a credible, substantial, and asserted utility has been disclosed above for the polypeptide PRO1759. Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, since Applicant has not provided evidence to demonstrate that the PRO1759 polypeptide has a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. It is noted that the instant specification is required to teach one skilled in the art how to make and use the PRO1759 polypeptide.

3. However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 28-32 and 39-40 would remain rejected under 35 U.S.C. § 112, first paragraph.

It is noted that specific issues of claims 28-32 and 39-40 (recitation of percent identity), were discussed under 35 U.S.C. § 112, first paragraph at pg 20-22 of the previous Office Action (06 October 2005), at pg 13-15 of the Office Action of 25 April 2005, and at pg 9-11 of the Office Action of 04 November 2004. However, Applicant did not specifically address the Examiner's issues in the response of 07 August 2006. The Examiner maintains the rejection for reasons already made of record.

Essentially, the specification does not teach any variant, fragment, or derivative of the PRO1759 polypeptide other than the full-length amino acid sequence of SEQ ID NO: 374. The specification also does not teach functional or structural characteristics of the polypeptide variants, fragments, and derivatives (including the extracellular domain) recited in the claims. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. A large quantity of experimentation would be required by the skilled artisan to generate the infinite number of derivatives recited in the claims and screen the same for activity.

Proper analysis of the Wands factors was provided in the previous Office Actions. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance

presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 U.S.C. § 112, first paragraph (written description)

4. Claims 28-32 and 39-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pg 22-25 of the previous Office Action (06 October 2005), at pg 15 of the Office Action of 25 April 2005 and at pg 11-13 of the Office Action of 04 November 2004.

It is noted that the specific issue of claims 28-32 and 39-40, namely recitation of percent identity, was discussed extensively under 35 U.S.C. § 112, first paragraph in the previous Office Actions. However, Applicant did not specifically address the Examiner's issues in the response of 07 August 2006. The Examiner maintains the rejection for reasons already made of record.

Essentially, Applicant has not described or shown possession of all polypeptides 80%, 85%, 90%, 95%, and 99% homologous to SEQ ID NO: 374, that still retain the function of SEQ ID NO: 374. Nor has Applicant described a representative number of species that have 80%, 85%, 90%, 95%, and 99% homology to SEQ ID NO: 374, such that it is clear that they were in

possession of a genus of polypeptides functionally similar to SEQ ID NO: 374. Even one skilled in the art could not envision the detailed chemical structure of all or a significant number of encompassed PRO1759 polypeptides, and therefore, would not know how to make or use them. In this case, the only factors present in the claims are a partial structure in the form of a recitation of percent identity, a requirement that the sequence be native, and a requirement that the encoding nucleic acids are amplified in lung or colon tumors. There is no identification of any particular portion of the structure that must be conserved in order to conserve the required function. Additionally, there is the issue of whether or not the single disclosed embodiment is actually amplified in lung or colon tumors (see rejection under 35 U.S.C. §§ 101 and 112, first paragraph, above). Clearly, such does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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BEB
Art Unit 1647
16 October 2006

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER